

### **REMARKS**

Applicants hereby reiterate the remarks presented in Applicant's Response of April 2, 2007 and hereby augment same with regard to Bartley (US Pat. No. 5,766,581).

Bartley et al is asserted to teach pegylation of one specific protein (MGDF) via branched or unbranched PEG (including monoethoxy polyethylene glycol) in the range of only 12-25 kDa to the N terminus of the lysine residue or via an amide bond at the N-terminus of the protein. Bartley is also asserted to teach pharmaceutical compositions of said peg-modified protein. Applicants respectfully traverse and overcome this rejection.

However, Bartley only discloses peg-modification of MGDFs (MP11.z and s) or megakaryocyte growth and development factors and related proteins. There is no correlation or apparent teaching of peg-modified MGDFs with any other unrelated protein, much less HGF or NK4. Contrary to the Examiner's assertion that it would be obvious to try the method of Bartley to the HGF of Date, there is no teaching in Bartley that its modification method would work on any other protein which is unrelated to MGDF protein. In fact, Bartley teaches the exact opposite: Bartley teaches that modifying other proteins is unpredictable.

In column 5, lines 21 to 23, Bartley et al. expressly admits and teaches that "it should be noted that the effect of modification of a particular protein **cannot be predicted**". (emphasis added) Thus, Bartley et al at best teach only how to modify just MGDF protein but do not teach how to modify HGF or NK4, respectively. Bartley again admits and teaches this unpredictability in column 6, lines 15 to 20:

"the ability to modify MGDF is unknown in the art since the susceptibility of each individual protein to modification is determined by the specific structural parameters of that protein. **Moreover, the effect of such a modification on the**

**biological properties of each protein is unpredictable from the art"**  
(emphasis added)

and further in lines 43 to 46 of the same column "for example, it has been shown that in the case of nonselective conjugation of superoxide dismutase with polyethylene glycol, several fractions of the modified enzyme were completely inactive (P. McGoff et al.)". The Bartley inventors themselves could not even predict the outcome of their own experiments as shown in column 23, lines 57 to 60, admitting that "however, the polymer/MGDF molecule disclosed herein may have additional activities, enhanced or reduced activities, or other characteristics, as compared to the non-derivatized molecule" (emphasis added).

Applicants' invention is directed to the attachment of one PEG-moiety with a molecular weight of 30 to 40 kDa to HGF/NK4 via an amide bond. Bartley et al only discloses the attachment of PEG to just one protein, MGDF. Bartley emphatically and expressly admits and recognizes the unpredictability of modifying any protein. Bartley therefore teaches away from using its method with any other protein!

The Examiner alleges in the Advisory Action that Bartley cites pegylation of some other proteins (col 5, lines 30-37) and thus concludes that pegylation of any protein is predictable. Such a conclusion is not consistent with Bartley, which states the complete opposite conclusion. Bartley unequivocally states in the very next column that "the susceptibility of each individual protein to modification is determined by the specific structural parameters of that protein. Moreover, the effect of such a modification on the biological properties of each individual protein is unpredictable from the art." (Col 6, lines 15-20).

Bartley is thus averring two factors. First, Bartley teaches that how a protein may be modified, or even if it can be modified, and the how of that modification "is determined by the specific structural parameters of that protein". Bartley teaches further

that “pegylation of protein molecules will generally result in a mixture of chemically modified protein molecules” or in other words a heterogeneous mixture of molecules with varying peg moieties attached thereto (col 6, lines 24-33). Bartley concludes that such mixtures and variability of said mixtures from lot to lot “would be disadvantageous when developing a therapeutic pegylated protein product” (Col 6, lines 40-42, emphasis added).

This leads to the second factor: the unpredictability of biological activity. Bartley again unequivocally states that in the development of a therapeutic pegylated protein product, “predictability of biological activity is important” (Col 6, lines 42-43) stating that for example “one cannot have such predictability if the therapeutic protein differs in composition from lot to lot” (Col 6, lines 51-52).

Bartley therefore teaches that a) modification of a protein depends first upon its specific structural parameters, b) that pegylation of a protein will generally result in a mixture of chemically modified protein molecules, c) that said mixture would be disadvantageous in developing a therapeutic pegylated protein product, and d) that predictability of biological activity of the therapeutic pegylated protein product is important and necessary. Bartley does not teach Applicants’ specific protein, does not teach how to modify Applicants’ specific protein, does not teach how to avoid a mixture of pegylated moieties of Applicants’ protein, and does not teach predictability of Applicants’ protein or of the peg-modified protein. Indeed, Bartley candidly admits it cannot teach any of these things at all as to other proteins as “the effect of modification of a particular protein cannot be predicted”. Contrary to the Examiner’s assertion of predictability (obviousness), Bartley instead teaches unpredictability: “the effect of such a modification on the biological properties of each protein is unpredictable from the art.”


Applicants respectfully submit that Bartley must be read in its entirety. Bartley unequivocally teaches that “modification on the biological properties of each protein is unpredictable from the art” (Bartley emphasis added). Bartley therefore acknowledges

and restates that a person of ordinary skill in the art is aware of this unpredictability. Furthermore, Bartley cautions and warns the person of ordinary skill in the art against predicting success of modifying one protein versus another: "it should be noted that the effect of modification of a particular protein cannot be predicted." One of ordinary skill in the art would not therefore look to the method of Bartley to modify a protein other than MGDF. Instead, one of ordinary skill in the art would heed the warning, caution and teaching of Bartley that "the effect of modification of a protein cannot be predicted".

Accordingly, Applicants respectfully submit that Claims 1, 5-6, 8 and 12-15 are in condition for allowance.

No further fee, other than the two-month extension of time, is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

  
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